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CLINICAL NEUROSCIENCES

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Title: CNS EFFECTS OF THE NEW BENZODIAZEPINES RO 48-6791 AND RO 48-8684 COMPARED TO MIDAZOLAM IN YOUNG AND ELDERLY VOLUNTEERS

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Introduction: Despite its advantages compared to other benzodiazepines (BZD) midazolam (M) shows a relatively slow onset of action and recovery which complicates or restricts its applications. According to preclinical investigations, the new BZD-agonists Ro 48-6791 and Ro 48-8684 promised to have more favorable properties with respect to control and potency. The objective of the present study was to investigate the pharmacodynamic profile of the new compounds using the EEG as a measure of the sedative-hypnotic effect.

Methods: After institutional approval and written consent, 11 young (24-28 yr) and 9 elderly (67-81 yr) male volunteers were enrolled in the present phase I study. The study design was randomized, cross-over and double-blind. Two consecutive infusion cycles consisting of an induction phase with linearly increasing plasma concentrations (15-30 min) followed by a plateau phase of 15 min were administered on a particular treatment day. The infusion rates were computer-controlled with a slope of 3, 10 and 40 ng/ml/min for Ro 48-6791, Ro 48-8684 and M, respectively. For the elderly the slopes were reduced to 50%. During and following the infusions the EEG (CATEEM®) was recorded as continuous pharmacodynamic measure to quantitate the hypnotic effect. In addition, clinical signs of anesthesia were obtained. Arterial blood samples were frequently drawn up to 6 hours after cessation of the second infusion. Plasma concentrations were analyzed using specific LC/MS/MS and GC methods. Nonlinear regression analysis (NONMEM®) was used to relate the median frequency of the EEG power spectrum to the plasma concentration by a sigmoid E_{max} model including an effect compartment to minimize the hysteresis between concentration and effect.

Results: For the young the total doses administered in the two infusion cycles were 26±3, 122±32 and 69±11 mg for Ro 48-6791, Ro 48-8684 and M, respectively. The elderly received 15±2, 69±14 and 36±6 mg. All compounds induced a delta dominated EEG with a minimum median frequency of about 2 Hz after an initial beta activation. As expected from previous studies, the new BZD are characterized by a higher potency as indicated by the smaller EC_{50} (table). All compounds show a very steep response curve and a distinct hysteresis between concentration and effect with a large interindividual variability. For the elderly, EC_{50} was decreased to 43%, 70% and 60% for M, Ro 48-6791 and Ro 48-8684, respectively. For the young as well as for the elderly, recovery was significantly faster after administration of the new BZD.

	Midazolam		Ro 48-6791		Ro 48-8684	
	young	elderly	young	elderly	young	elderly
E_{max} [Hz]	6.8 (1.6)	5.5 (1.8)	6.9 (1.7)	5.4 (1.2)	7.3 (1.9)	4.5 (1.8)
EC_{50} [ng/ml]	531 (221)	228# (54)	62* (28)	43* (15)	277+ (147)	167+ (29)
γ	28 (17)	39 (15)	14 (11)	33 (19)	25 (20)	34 (16)
k_{eo} [min^{-1}] †	0.09	0.08	0.14	0.10	0.07	0.10
recovery [min after stop of infusion]	54 (26)	46 (20)	18* (9)	25* (14)	28+ (11)	24+ (9)

Tab.: *Pharmacodynamics of midazolam, Ro 48-6791 and Ro 48-8684 (mean and sd, median †). p<0.05 *: Ro 48-6791 vs. M, +: Ro 48-8684 vs. M, #: young vs. elderly*

Conclusion: When compared with midazolam the new benzodiazepines are outlined by a faster recovery improving the control. Concerning potency Ro 48-6791 has marked advantages when compared to M and Ro 48-8684, respectively, and should be followed in further clinical studies.

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TITLE: Changes in cerebral blood flow velocities during induced hypotension for embolization of brain arteriovenous malformations (AVM)

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Deliberate hypotension is used for embolization of AVMs to slow the flow through the fistula and control the distribution of the glue during the injection (1). However, the optimal decrease in blood pressure is usually determined subjectively. The aim of this study was to measure the flow reduction induced by hypotension in the vessel supplying the brain AVM using transcranial doppler ultrasonography (TCD)

METHODS: 10 patients undergoing 13 embolizations of brain AVMs were included in the study. All patients were intubated and ventilated under general anesthesia (PCO_2 before hypotension: 32±3 mm Hg). Mean arterial pressure (MAP) was measured through the femoral artery introducer sheath. Controlled hypotension was induced with a combination of isoflurane (0.6 to 0.8 %), labetalol (15 to 25 mg) and esmolol as needed. Mean cerebral blood flow velocities (CBFV) and pulsatility indexes (PI) were measured using an EME-TC 2-64 TCD. The measurements were performed on the parent vessel of the AVM ($CBFV_{AVM}$) and on the middle cerebral artery controlateral to the AVM. CBFV was noted in % of the value measured under general anesthesia just before hypotension. The search for correlation used linear regression analysis.

RESULTS: Before hypotension, CBFV and PI on the AVM side were respectively 106 ± 31 cm.s-1 and 0.52 ± 0.13, and 40 ±19 cm.s-1 and 1.08 ± 0.28 on the controlateral MCA. There was not any correlation between CBFV and MAP on the normal MCA but the correlation was significant on the parent vessel of the AVM (Fig 1). There was a significant correlation between PI and MAP on the normal MCA ($r=0.44$; $p<0.01$) but there was not any correlation between PI and MAP on the AVM parent vessel.

DISCUSSION: The relations between CBFV or PI and MAP in this study confirms that autoregulation is impaired in AVM feeding vessels (2). When the MAP decreased under 50 mm Hg, we observed a trend to a decrease in $CBFV_{MCA}$, indicating that the lower limit of autoregulation was reached in the normal brain. In conclusion, TCD can be used to determine the hypotension needed for the embolization of brain AVMs and to avoid a decrease of MAP beyond the lower level of autoregulation in the normal brain.

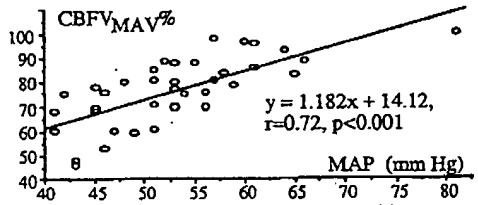

Fig 1: Changes in CBFV and MAP on the AVM side

References
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2. J Neurosurg, 67:822-831,1987